

## REMARKS

Claims 1-24 are pending in the application. Claims 1-4 and 8-24 were withdrawn from consideration, leaving claims 5-7 subject to examination. Claims 5-7 were objected to due to an issue of claim dependency, rejected under 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 102(b), and provisionally rejected under the judicially-created Doctrine of Obviousness Type Double Patenting. The objection and each of the rejections are addressed as follows.

First, Applicants note that the declaration was indicated as being defective, on the basis that non-initialed and/or non-dated alterations were made to the declaration. In particular, the Examiner notes that the city of the residence of inventor Juan Arroyo has been altered but not initialed. 37 C.F.R. § 1.52(c)(1) specifies that any alteration of the application filing papers must be made before signing of the accompanying declaration and should be initialed or signed and dated by the Applicant on the same sheet of paper. In the present case, the change to inventor Arroyo's address was made by him at the time that he signed and dated the document, which should be sufficient to meet the requirements of 37 C.F.R. § 1.52(c)(1), as noted above.

Applicants thus request reconsideration of the requirement for a new oath or declaration.

Applicants further note that claim 5 has been amended to specify that the claimed chimeric flaviviruses are present in the form of a vaccine. Support for this amendment can be found, for example, on pages 10-11 of the application. In addition, new claims specifying that the viruses include a hinge region mutation that is a reversion to a wild-type sequence at envelope position 279 have been added (claims 25-27). These claims are supported, for example, at pages 12-23 of the application. No new matter is added by the amendments.

The objection and rejections are now each addressed.

### Claim Objection

Claims 5-7 were objected to as depending from what the Examiner has indicated are rejected claims. As the claims from which claims 5-7 depend were not subject to examination, Applicants have assumed that these claims were objected to for depending from withdrawn claims. In any case, to meet this objection, claim 5, from which claims 6 and 7 depend, has been amended to include the limitations of claim 1, from which it formerly depended. Applicants thus request that this objection be withdrawn.

### Rejection under 35 U.S.C. § 112, first paragraph

Claims 5-7 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claims encompass a large genus of flavivirus chimeras, with respect to which Applicants have not demonstrated adequate possession. The Examiner further states that the specification must provide sufficient identifying characteristics of the claimed genus. This rejection is respectfully traversed.

First, Applicants note that the Examiner states that the embodiments that are adequately described include chimeras having the E279 reversion of Japanese encephalitis virus. Applicants thus request separate consideration of the claims specifying a mutation at this position (i.e., new claims 25-27).

As to the remaining claims, Applicants note that these claims have been amended to specify that the viruses of these claims are chimeric flaviviruses that include an envelope protein from an attenuated Japanese encephalitis virus, which includes a hinge region mutation in any one (or more) of amino acids corresponding to amino acids 48-61, 127-131, and 196-283 of a

yellow fever virus, that decreases viscerotropism of the chimeric flavivirus. Applicants further note that the flavivirus envelope hinge region, which includes the specified amino acids, is well-defined in the art. Indeed, the crystal structure of this region of a representative flavivirus was published more than ten years ago (Rey et al., *Nature* 375:291-298, 1995). Further, for the Examiner's reference, Applicants submit herewith a diagram showing the envelope structure of Japanese encephalitis virus, which was prepared by homology modeling using the structure described in the Rey reference, noted above.

Applicants have thus specified mutations in a very well-defined region of Japanese encephalitis virus. Based on this information, Applicants submit that those of skill in the art would be aware of fact that the present Applicants were in possession of the claimed invention. Applicants have also provided sufficient identifying characteristics of the genus, as the positions of the mutations are clearly set forth in the claims. Applicants thus respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 5-7 were rejected under 35 U.S.C. § 102(b) as being anticipated by Chambers et al., *J. Virology* 73(4):3095-3101, 1999. Referring to tables 3 and 4 of Chambers, the Examiner states that this reference teaches that the JEV envelope region has a mutation (i.e., a reversion) at position 279 of the hinge region. Applicants request that this rejection be withdrawn.

As is noted above, the present claims have been amended to specify that the viruses of the claims are chimeric flaviviruses that include an envelope protein from an attenuated Japanese encephalitis virus, in which there is a hinge region mutation that decreases viscerotropism of the

chimeric flavivirus. The only chimeric flaviviruses described in the Chambers reference include envelope sequences of the attenuated SA14-14-2 strain (e.g., YF/JE-S) or the wild-type Nakayama strain (e.g., YF/JE-N). The chimeras including SA14-14-2 sequences do not anticipate the present claims, as the envelope hinge region sequences of these chimeras do not include mutations that decrease viscerotropism. The chimeras including Nakayama sequences also do not anticipate the present claims, as the envelope proteins of these chimeras are not from an attenuated strain. Applicants thus submit that rejection over the Chambers reference should be withdrawn.

Claims 5-7 were also rejected under 35 U.S.C. § 102(b) as being anticipated by Arroyo et al., *J. Virology* 75(2):934-942, 2001. The Examiner states that Arroyo discloses a yellow fever virus/Japanese encephalitis virus chimera that includes a lysine at position 279 of the hinge region. In response, we note that the current claims specify that the claimed viruses are in the form of a vaccine (see amendment to claim 5, above). The focus of the study of Arroyo is the characterization of the contribution of amino acids differing between vaccine (SA 14-14-2) and wild-type (Nakayama) strains of Japanese encephalitis virus to neurovirulence. In the Arroyo study, the amino acids are reverted individually and in combination (see, e.g., Table 3) to assess the impact of reversions on neurovirulence. Arroyo does not suggest use of the revertants, such as the E279 revertant, in the form of vaccines. Arroyo therefore does not anticipate the present claims.

Applicants further note that Arroyo does not render the present claims obvious, as Arroyo teaches that reversion of E279 increases neurovirulence (see, e.g., Table 3, and page 939, last paragraph of the left column: "...reversion at E<sub>279</sub> appeared to increase neurovirulence...").

Thus, based on this reference, there would not have been motivation to use the E279 revertant in the form of a vaccine. However, the experiments described in the present application show that the E279 revertant has unexpectedly beneficial properties with respect to viscerotropism, which in turn render it to be a vaccine candidate (see, e.g., pages 12-23). Thus, Applicants submit that an obviousness rejection of claims specifying the E279 revertant should not be made over the Arroyo reference.

Provisional Obviousness-Type Double Patenting Rejection

Claims 5 and 6 were provisionally rejected under the judicially-created Doctrine of Obviousness-Type Double Patenting over claims 1, 2, and 4 of co-pending application no. 10/345,036. When the only rejection remaining in a case is a provisional double patenting rejection, an application should be allowed to issue. M.P.E.P. § 822.01. In view of the amendments and remarks provided herein, Applicants submit that all of the grounds of rejection in this case, other than the double patenting rejection, have been met. Accordingly, the double patenting rejection should be withdrawn and the case allowed to issue.

CONCLUSION

Applicants submit that the claims are in condition for allowance and such action is respectfully requested. Although no charges are believed to be due, if there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: October 20, 2006

Susan M. Michaud  
Susan M. Michaud, Ph.D.  
Reg. No. 42,885

Clark & Elbing LLP  
101 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045